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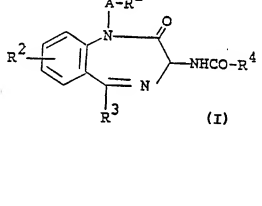

(I)

(57) Abstract

Benzodiazepine derivatives of formula (I), wherein R^1 is heterocyclic group which may have one or more suitable substituent(s), or cyano, R^2 is hydrogen or halogen, R^3 is aryl which may have one or more suitable substituent(s), R^4 is aryl which may have one or more suitable substituent(s), etc., and A is lower alkylene, and pharmaceutically acceptable salts thereof which are useful as a medicament.

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DESCRIPTION

BENZODIAZEPINE DERIVATIVES

TECHNICAL FIELD

This invention relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

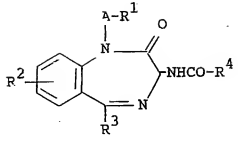
Some benzodiazepine derivatives have been known as described, for example, in European Patent Application Publication No. 349949 and U.S. Patent 4,820,834.

DISCLOSURE OF INVENTION

This invention relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof which are cholecystokinin (CCK) antagonists and therefore useful as therapeutical and/or preventive agents for emesis, pancreatitis, disorders of appetite requlatory systems, pain, insulinoma, gastroparesis, carcinoma of pancreas, gallbladder disease (e.g. acute cholecystitis, calculus, etc.), disorders associated with intenstinal smooth muscle hyperactivity (e.g. irritable bowel syndrome, sphincter spasm, etc.), hyperinsulinemia, dyspepsia, nausea, etc.

The benzodiazepine derivatives of this invention can be represented by the following formula (I) :



(I)

wherein R^1 is heterocyclic group which may have one or more suitable substituent(s), or cyano,

R^2 is hydrogen or halogen,

R^3 is aryl which may have one or more suitable substituent(s),

R^4 is aryl which may have one or more suitable substituent(s), ar(lower)alkenyl which may have one or more suitable substituent(s), arylamino which may have one or more suitable substituent(s), heteromonocyclic group which may have one or more suitable substituent(s), quinolyl, isoquinolyl, cinnolinyl, indolyl, or quinoxalinyl, and

A is lower alkylene,

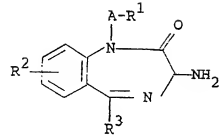
with proviso that when R^4 is indolyl, then

(i) R^1 is tetrazolyl which may have one or more suitable substituent(s) and R^3 is halophenyl or

(ii) R^1 is imidazolyl which may have one or more suitable substituent(s), R^3 is halophenyl and A is ethylene.

According to the present invention, the new benzodiazepine derivatives (I) can be prepared by the processes which are illustrated in the following scheme.

Process 1



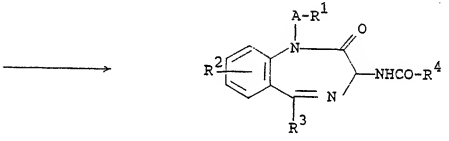
(II)

or its reactive derivative at the amino group, or a salt thereof

+

(III)

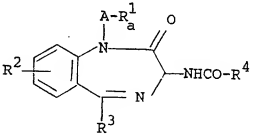
or its reactive derivative, or a salt thereof



(I)

or a salt thereof

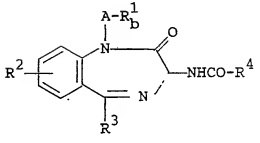
Process 2



(Ia)

or a salt thereof

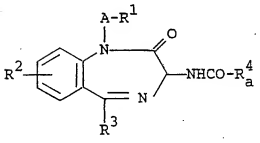
Elimination reaction of the imino protective group



(Ib)

or a salt thereof

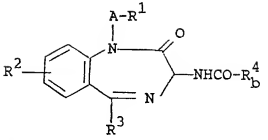
Process 3



(Ic)

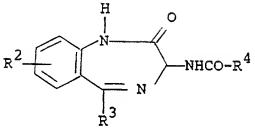
or a salt thereof

Reduction



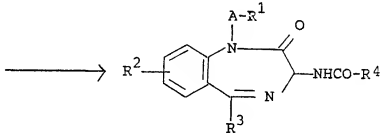
(Id)
or a salt thereof

Process 4



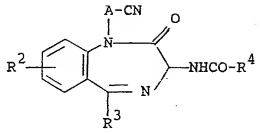
(IV)
or a salt thereof

+ X-A-R^1 (V)
or a salt thereof



(I)
or a salt thereof

Process 5



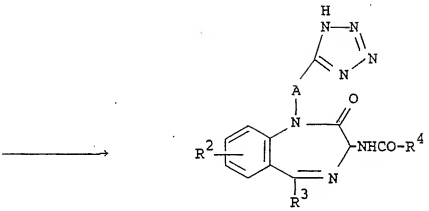
(Ie)

or a salt thereof

+ HN_3

(VI)

or a salt thereof



(If)

or a salt thereof

wherein R^1, R^2, R^3, R^4 and A are each as defined above, R^1_a is heterocyclic group having a protected imino group of the formula :

(in which R^6 is imino protective group)

in its hetero ring, which may have one or

more suitable substituent(s),

R^1_b is heterocyclic group having an imino group of the formula : 

in its hetero ring, which may have one or more suitable substituent(s),

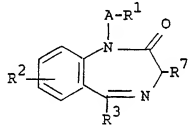
R^4_a is ar(lower)alkenyl having a nitro group,

R^4_b is ar(lower)alkenyl having an amino group and

X is an acid residue.

The starting compounds (II) and (IV) can be prepared by the following processes.

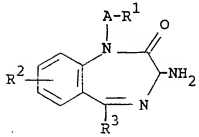
Process A



(VII)

or a salt thereof

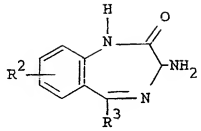
↓ Elimination reaction of the amino protective group



(II)

or a salt thereof

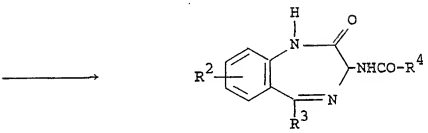
Process B



(VIII)
or its reactive derivative at the amino group, or a salt thereof

+

(III)
or its reactive derivative, or a salt thereof



(IV)
or a salt thereof

wherein R^1, R^2, R^3, R^4 and A are each as defined above, and
R^7 is protected amino.

The starting compound (VII) or a salt thereof can be prepared by the methods disclosed in the Preparations 1-3, 6 and 7 described later or similar manners thereto.

With regard to the object compound (I), in case that the compound (I) has the group of the formula :

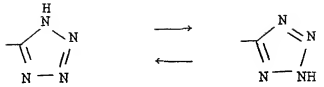
in R^1, said group can also exist in the tautomeric form and such tautomeric equilibrium can be represented by the following scheme.

(A) (B)

Both of the above tautomeric isomers are included within the scope of the present invention. In the present specification and claim, the compounds including the group of such tautomeric isomers are represented for the convenient sake by one expression of the group of the formula (A).

Further, in case that the compound (I) has the group of the formula :

in R^1, said group can also exist in the tautomeric form and such tautomeric equilibrium can be represented by the following scheme.



(C) (D)

Both of the above tautomeric isomers are included within the scope of the present invention. In the present specification and claim, the compounds including the group of such tautomeric isomers are represented for the convenient sake by one expression of the group of the formula (C).

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon

atom(s), unless otherwise indicated.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like. And especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, dihydropyridazinyl, tetrahydropyridazinyl, triazolyl (e.g. 1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, isoindolinyl, indolizynyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g. tetrazolo-[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, etc.;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, dihydroisoxazolyl, oxadiazolyl, (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2

oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, 1,3-thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.;
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
unsaturated 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example furyl, etc.;
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc. and the like.

Suitable "substituent" in the terms "heterocyclic group which may have one or more suitable substituent(s)" and "heteromonocyclic group which may have one or more suitable substituent(s)" may include amino, protected amino as exemplified below, oxo, hydroxy, imino protective group as exemplified below, lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, t-pentyl, hexyl, etc.) and the like.

Suitable "protected amino" may include acylamino and the like.

Suitable "imino protective group" may include acyl, mono(or di or tri)phenyl(lower)alkyl (e.g. trityl, etc.) tetrahydropyranyl and the like.

Suitable "acyl" and "acyl moiety" in the term "acylamino" may include aliphatic acyl group and acyl group containing an aromatic or heterocyclic ring.

And, suitable examples of the said acyl may be lower

alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);
lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.);
lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.);
arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.);
aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarbonyl, etc.);
ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.);
ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

The acyl moiety as stated above may have at least one suitable substituent(s) such as halogen (e.g. chlorine, bromine, fluorine and iodine), amino, protected amino (e.g. lower alkanoylamino, phenylthioureido, etc.), or the like.

Suitable "acid residue" may include halogen and the like.

Suitable "halogen" may include chlorine, bromine, fluorine and iodine.

Suitable "aryl" and "aryl moiety" in the terms "ar(lower)alkenyl" and "arylamino" may include phenyl, naphthyl and the like.

Suitable "substituent" in the terms "aryl which may have one or more suitable substituent(s)", ar(lower)alkenyl which may have one or more suitable substituent(s)" and "arylamino which may have one or more suitable substituent(s)" may include hydroxy, protected

hydroxy as exemplified below, nitro, lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy, etc.), amino, protected amino as exemplified above, lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, t-pentyl, hexyl, etc.), halogen as exemplified above, and the like.

Suitable "lower alkenyl moiety" in the term "ar(lower)alkenyl" may include vinyl, allyl, 1-propenyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl and the like.

Suitable "heteromonocyclic group" may include saturated or unsaturated heteromonocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like. And, especially preferable heteromonocyclic group may be heteromonocyclic group such as

unsaturated 3 to 8-membered heteromonocyclc group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, dihydropyridazinyl, tetrahydropyridazinyl, triazolyl (e.g. 1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.; saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.; unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, dihydroisoxazolyl, oxadiazolyl, (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; saturated 3 to 8-membered heteromonocyclic group

containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;
unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, 1,3-thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazoylyl, 1,2,3-thiadiazolyl, etc.;
saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
unsaturated 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example furyl, etc.;
unsaturated 3 to 8-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.;
and the like.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene or the like, preferably one having 1 to 4 carbon atom(s).

Preferable "heterocyclic group" in the terms "heterocyclic group having a protected imino group of the formula :  (in which R^6 is imino protective group) in its hetero ring" and "heterocyclic group having an imino group of the formula : in its hetero ring" may include

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, dihydropyridaziny', tetrahydropyridazinyl, triazolyl (e.g. 1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl

(e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.; saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.; and the like.

The preferred embodiments of the object compound (I) are as follows.

R^1 is heterocyclic group (more preferably unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), most preferably tetrazolyl or imidazolyl) which may have one to three (more preferably one) suitable substituent(s) [more preferably tetrazolyl or imidazolyl, each of which may have an imino protective group; most preferably tetrazolyl or imidazolyl, each of which may have mono(or di or tri)phenyl(lower)alkyl], or cyano;

R^2 is hydrogen;

R^3 is aryl (more preferably phenyl) which may have one to three (more preferably one) suitable substituent(s) [more preferably phenyl or halophenyl];

R^4 is aryl (more preferably phenyl or naphthyl) which may have one to three (more preferably one or two) suitable substituent(s) [more preferably phenyl or naphthyl, each of which may have one or two substituent(s) selected from the group consisting of halogen and amino; most preferably naphthyl, dihalophenyl or phenyl having halogen and amino], ar(lower)alkenyl (more preferably phenyl(lower)alkenyl) which may have one to three (more preferably one) suitable substituent(s) [more preferably phenyl(lower)alkenyl which may have amino or nitro; most preferably nitrophenyl(lower)alkenyl

or aminophenyl(lower)alkenyl], arylamino (more preferably phenylamino) which may have one to three (more preferably one) suitable substituent(s) [more preferably phenylamino which may have lower alkyl or halogen; most preferably lower alkylphenylamino or halophenylamino], heteromonocyclic group (more preferably pyridyl or tetrahydropyridazinyl) which may have one to three (more preferably one) suitable substituent(s) [more preferably pyridyl, or tetrahydropyridazinyl which may have an oxo group; most preferably pyridyl, or tetrahydropyridazinyl having an oxo group], quinolyl, isoquinolyl, cinnolinyl, indolyl or quinoxalinyl, and

A is lower alkylene (more preferably C_1-C_4 alkylene),

with proviso that when R^4 is indolyl, then

(i) R^1 is tetrazolyl and
R^3 is halophenyl or

(ii) R^1 is imidazolyl which may have mono(or di or tri)-phenyl(lower)alkyl,
R^3 is halophenyl and
A is ethylene.

The processes for preparing the object compound (I) and the starting compounds of the present invention are explained in detail in the following.

Process 1 :

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as

aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

Suitable salts of the compound (II) and (III) can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, isocyanate and the like. The suitable example may be an acid chloride, an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine,

1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.), isocyanate of the formula : R^5-N=C=O (in which R^5 is aryl which may have one or more suitable substituent(s)), and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (III) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphsphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of

N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.;
or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 2

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to elimination reaction of the imino protective group. Suitable method of this reaction may include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or

the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], N,N-dimethylformamide, methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence

the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process 3

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to reduction reaction. This reduction reaction can be referred to that of the aforementioned Process 2.

Process 4

The compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

Suitable salts of the compounds (IV) and (V) can be referred to the ones as exemplified for the compound (I).

This reaction is usually carried out in the presence of base.

Suitable base may include an inorganic base such as alkali metal hydride (e.g. sodium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal

phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine or the like.

This reaction is usually carried out in a solvent such as alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 5

The compound (If) or a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with the compound (VI) or a salt thereof.

Suitable salts of the compounds (Ie) and (If) can be referred to the ones as exemplified for the compound (I).

Suitable salts of the compound (VI) may include an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and the like.

The reaction is usually carried out in a conventional solvent such as

1-methyl-2-pyrrolidinone, N,N-dimethylformamide, dichloromethane, ethylene chloride or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

Process A

The compound (II) or a salt thereof can be prepared by subjecting the compound (VII) or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compound (VII) can be referred to the ones as exemplified for the compound (I).

The elimination reaction is carried out in accordance with a conventional method such as hydrolysis; reduction; Edman's method (phenyl isothiocyanate method); or the like. The hydrolysis may include a method using an acid or base or hydrazine and the like. These methods may be selected depending on the kind of the protective groups to be eliminated.

Among these methods, hydrolysis using an acid is one of the most common and preferable method for eliminating the protective groups such as substituted or unsubstituted alkoxycarbonyl, for example, tert-pentyloxycarbonyl, lower alkanoyl (e.g. formyl, acetyl, etc.), cycloalkoxycarbonyl, substituted or unsubstituted aralkoxycarbonyl, aralkyl (e.g. trityl), substituted phenylthio, substituted aralkylidene, substituted alkylidene, substituted cycloalkylidene or the like.

Suitable acid includes an organic or inorganic acid such as formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrochloric acid and the like, and the most suitable acid is an acid which can easily be removed from the reaction mixture by a conventional manner such as distillation under reduced pressure, for example, formic acid, trifluoroacetic acid, hydrochloric acid, etc. The acids can be selected according to the kind of the protective group to be eliminated.

The elimination reaction reaction using trifluoroacetic acid may be carried out in the presence of anisole. The hydrolysis using hydrazine is commonly applied for eliminating a phthaloyl, succinyl type amino-protective group.

The elimination using base is used for eliminating an acyl group such as trifluoroacetyl. Suitable base may

include an inorganic base and an organic base.

The reductive elimination is generally applied for eliminating the protective group, for example, haloalkoxycarbonyl (e.g. trichloroethoxycarbonyl, etc.), substituted or unsubstituted aralkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), 2-pyridylmethoxycarbonyl, etc. Suitable reduction may include, for example, reduction with an alkali metal borohydride (e.g. sodium borohydride, etc.), reduction with a combination of a metal (e.g. tin, zinc, iron, etc.) or the said metal together with a metal salt compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and catalytic reduction. Suitable catalyst includes a conventional one, for example, Raney nickel, platinum oxide, palladium on carbon and the like.

Among the protective groups, the acyl group can generally be eliminated by hydrolysis. Especially, halogen substituted-alkoxycarbonyl and 8-quinolyloxycarbonyl groups are usually eliminated by treating with a heavy metal such as copper, zinc, or the like.

The reaction is usually carried out in a conventional solvent such as water, chloroform, methylene chloride, alcohol (e.g., methanol, ethanol, etc.), tetrahydrofuran or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and may suitably be selected in accordance with the kind of the amino protective group and the elimination method as mentioned above, and the reaction is usually carried out under a mild condition such as under cooling or at slightly elevated temperature. Among the protective groups, the acyl group derived from α-amino acid can be eliminated by Edman's method.

Process B

The compound (IV) or a salt thereof can be prepared by reacting the compound (VIII) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative or a salt thereof.

The reaction is carried out by substantially the same method as that of Process 1, and therefore the reaction method and conditions are to be referred to said Process 1.

The object compound (I) and pharmaceutically acceptable salts thereof are CCK antagonists and therefore useful as therapeutical agents for emesis, pancreatitis, etc.

Further, it is expected that the object compound (I) and pharmaceutically acceptable salts thereof have gastric antagonism and are useful as therapeutical and/or preventive agents for ulcers, excess gastric secretion, Zollinger-Ellison Syndrome, etc.

In order to show the utility of the object compound (I), the pharmacological activity of the representative compound thereof is shown in the following.

[I] Test Compound :

(3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-[(E)-3-(2-aminophenyl)propenoylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride
[hereinafter referred to as test compound A]

[II] Test :

CCK receptor antagonism in isolated fundic circular muscle from guinea pig stomach

Test Method

The strip of circular muscle from guinea pig stomach was suspended in 25 ml organ bath containing Krebs'

bicarbonate solution (NaCl 118mM, KCl 4.8mM, KH_2PO_4 1.2mM, $MgSO_4$ 1.2mM, $CaCl_2$ 2.5mM, $NaHCO_3$ 25mM, glucose 11mM and bovine serum albumin 0.1%) maintained at 37°C and gassed with 95% O_2 and 5% CO_2.

The strip was placed under an initial tension of 0.5 g and equilibrated for 60 minutes during which the bath volume was replaced every 15 minutes. Isometric contraction was measured using a force transducer. CCK-8 (3.2×10^{-7}M) was added to the bathing solution and the contractile force was measured. After washing out CCK-8, it stood for about 15 minutes until contractile force became plateau. Then test compound A (1×10^{-6}M) was added. 5 minutes later, CCK-8 was added and the contractile force was recorded. CCK antogonism was calculated by comparing the contractile force induced by CCK in the absence or presence of test compound A.

Test Result

Inhibition (%) : 89.9

The object compound (I) or pharmaceutically acceptable salts thereof can usually be administered to mammals including human being in the form of a conventional pharmaceutical composition such as capsule, micro-capsule, tablet, granule, powder, troche, syrup, aerosol, inhalation, solution, injection, suspension, emulsion, suppository or the like, and the most suitable dosage form is injection.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g. sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate calcium carbonate, etc.), binding agent (cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone,

gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g. starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycole-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g. magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g. citric acid, mentol, glycine, orange powders, etc.), preservative (e.g. sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g. citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g. methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g. water), base wax (e.g. cacao butter, polyethyleneglycol, white petrolatum, etc.).

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The following Preparations and Examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of (3RS)-3-phthalimido-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (21.17 g) in N,N-dimethylformamide (400 ml) was added gradually sodium hydride (2.0 g, 60% suspension in mineral oil) under cooling in an ice-bath and nitrogen atmosphere. The mixture was stirred under the same conditions for 0.5 hour and at ambient temperature for 1 hour. The mixture was cooled in ice-bath and a solution of chloroacetonitrile (3.48 ml) in N,N-dimethylformamide (5 ml) was added dropwise thereto. The mixture was stirred for 1 hour at the same temperature and at ambient temperature overnight. To the reaction mixture was added acetic acid (3.5 g) under cooling and the resultant mixture was poured into a mixture of ethyl acetate and water under stirring. The mixture was adjusted to pH 7.5 with aqueous sodium bicarbonate. The crystals were collected by filtration and washed with cold ethyl acetate to give (3RS)-3-phthalimido-1-cyanomethyl-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (20.9 g).

mp : 260°C (dec.)

IR (Nujol) : 2160, 1776, 1725, 1700, 1604 cm^{-1}

NMR (DMSO-d_6, δ) : 5.15 (2H, ABq, J=24.6Hz, 17.8Hz), 5.83 (1H, s), 7.2-8.1 (12H, m)

Preparation 2

A mixture of (3RS)-3-phthalimido-1-cyanomethyl-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (20.0 g), sodium azide (8.43 g) and triethylamine hydrochloride (8.92 g) in N-methyl-2-pyrrolidone (350 ml) was heated at 145°C under stirring for 3.5 hours. After cooling to ambient temperature, the mixture was poured into 5% hydrochloric acid (500 ml) and ice. The resultant precipitates were collected by filtration, washed with cold water several times and dried over phosphorus

pentoxide under reduced pressure to afford (3RS)-3-phthalimido-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (18.07 g).

IR (Nujol) : 1778, 1720, 1693, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 5.46 (2H, s), 5.85 (1H, s), 7.2-8.0 (13H, m)

Preparation 3

To a solution of (3RS)-3-phthalimido-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (18.07 g) and trityl chloride (10.99 g) in N,N-dimethylformamide (330 ml) was dropwise added a solution of triethylamine (4.6 g) in N,N-dimethylformamide (10 ml) under stirring and cooling in an ice-bath. The mixture was stirred for 20 minutes under the same conditions and at ambient temperature overnight. The reaction mixture was poured into an ice-water (500 ml), and the resultant precipitates were collected by filtration, washed with water and dried over phosphorus pentoxide under reduced pressure to afford (3RS)-3-phthalimido-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (33.41 g) as white powder.

IR (Nujol) : 1778, 1723, 1695, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 5.56 (2H, ABq, J=16.0Hz, 52.6Hz), 5.80 (1H, s), 6.8-8.1 (27H, m)

Preparation 4

To a suspension of (3RS)-3-phthalimido-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (33.4 g) in tetrahydrofuran (500 ml) was added hydrazine hydrate (1.90 g) under stirring at ambient temperature. The mixture was stirred for 2 hours at the same temperature and refluxed under

stirring for 2 hours. The reaction mixture was cooled in an ice-bath and the resultant precipitates were filtered off. The filtrate and the washings were combined and evaporated to afford a residue, which was stirred in ethyl acetate and filtered. The filtrate and washings were combined and evaporated to give white powder (14.43 g) of (3RS)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one.

IR (Nujol) : 3350, 1686, 1597, 760, 700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.95 (2H, br s), 4.62 (1H, s), 5.42 (2H, ABq, J=19.6Hz, 15.8Hz), 6.8-7.6 (23H, m)

Preparation 5

The following compound was obtained according to a similar manner to that of Preparation 4.

(3RS)-3-Amino-1,3-dihydro-5-phenyl-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one

mp : 132-135°C

IR (Nujol) : 3375, 1680, 1595, 1575, 1560 cm^{-1}

NMR ($CDCl_3$, δ) : 2.72 (2H, s), 4.55 (1H, s), 5.46 (2H, ABq, J=16Hz, 51Hz), 6.90-6.70 (6H, m), 7.15-7.50 (18H, m)

Preparation 6

To a solution of (3RS)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (11.54 g) and N-t-butoxycarbonyl-L-phenylalanine (5.42 g) in N,N-dimethylformamide (200 ml) were added successively 1-hydroxybenzotriazole (2.76 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.91 g) and triethylamine (2.36 g) under stirring at ambient temperature. The mixture was stirred under the same conditions for 4.5 hours and then poured

into water (1.5 ℓ) under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The resultant precipitates were collected by filtration, washed with water and dried over phosphorus pentoxide under reduced pressure to give a mixture (16.29 g) of (3R)-3-[[(2S)-2-t-butoxycarbonylamino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one and (3S)-3-[[(2S)-2-t-butoxycarbonylamino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one.

mp : 108-114°C

IR (Nujol) : 3330, 1700, 1690, 1675, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.28 (9H, s), 2.65-2.9 (1H, m), 3.0-3.2 (1H, m), 4.40 (1H, m), 5.33-5.41 (2H, m), 5.39, 5.40 (1H, each d, J=8Hz), 5.58 (2H, ABq, J=16.8Hz, 82.2Hz), 6.8-7.95 (14H, m), 9.25, 9.37 (1H, each d, J=8Hz)

Preparation 7

A mixture of a mixture (16.2 g) of (3R)-3-[[(2S)-2-t-butoxycarbonylamino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one and (3S)-3-[[(2S)-2-t-butoxycarbonylamino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one and 4N solution of hydrogen chloride in ethyl acetate (200 ml) was stirred at ambient temperature for 5 hours. The mixture was concentrated in vacuo to give a residue, which was dissolved in methanol (100 ml) and neutralized with an ethanolic ammonia. The mixture was concentrated in vacuo to dryness. The residue was subjected to column chromatography on silica gel with an eluent ($CHCl_3$:CH_3OH = 10:1). The fractions containing

the object compound were combined and evaporated to give an amorphous mass, which was suspended in diisopropyl ether and collected by filtration to give (3S)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (4.57 g).

NMR (DMSO-d_6, δ) : 2.91 (1H, dd, J=14.0Hz, 8.4Hz), 3.20 (1H, dd, J=4Hz, 14.0Hz), 4.13 (1H, dd, J=4Hz, 8.4Hz), 5.26 (2H, ABq, J=15.4Hz, 31.6Hz), 5.39 (1H, d, J=8.0Hz), 7.1-7.35 (10H, m), 7.52-7.66 (4H, m), 7.96 (1H, d, J=8.4Hz), 9.77 (1H, d, J=8.0Hz)

The fractions containing the other object compound were combined and evaporated to give an amorphous mass, which was suspended in diisopropyl ether and collected by filtration to give (3R)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (4.76 g).

NMR (DMSO-d_6, δ) : 3.0-3.17 (1H, m), 3.57-3.64 (1H, m), 3.0-4.1 (2H, broad), 4.21 (1H, t, J=4.2Hz), 5.19 (2H, ABq, J=15.6Hz, 70.1Hz), 5.38 (1H, d, J=8.3Hz), 7.16-7.4 (10H, m), 7.51-7.67 (4H, m), 7.97 (1H, d, J=8.2Hz), 9.78 (1H, d, J=8.3Hz)

Preparation 8

To a solution of (3S)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (4.57 g), and triethylamine (0.974 g) in dried tetrahydrofuran (45 ml) was added phenyl isothiocyanate (2.54 g) under stirring at ambient temperature. The mixture was stirred for 2 hours at ambient temperature and for 1 hour at 50°C. To the reaction mixture was added 1N-hydrochloric acid (9.64 ml) under ice cooling.

The mixture was concentrated in vacuo to give a residue, which was extracted with ethyl acetate. The extract was washed with water twice and dried over magnesium sulfate. Removal of the solvent in vacuo afforded an amorphous mass (7.23 g), which was powdered by stirring in diisopropyl ether for 3 hours. The resultant powder was collected by filtration and washed with diisopropyl ether to give (3S)-3-[[(2S)-2-{N'-(phenyl)thioureido}-3-phenylpropanoyl]amino]-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (5.63 g). The product obtained above was suspended in tetrahydrofuran (35 ml) and 4N-hydrogen chloride in ethyl acetate (33.5 ml) was added dropwise thereto under ice-cooling. The mixture was stirred for 5 hours and then evaporated in vacuo to give a viscous oil, which was washed with ethyl acetate by stirring for 3 hours. The resultant powder was collected by filtration, and dried under reduced pressure to give (3S)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one hydrochloride (2.91 g).

$[\alpha]_D^{30}$ = -36.36° (C=0.495, CH_3OH)

Preparation 9

The following compound was obtained according to a similar manner to that of Preparation 8.

(3R)-3-Amino-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one hydrochloride

$[\alpha]_D^{30}$ = + 33.46° (C=0.505, CH_3OH)

Preparation 10

To a suspension of (3RS)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (2.0 g) in methylene chloride (30 ml) was added dropwise

triethylamine (1.61 g) under stirring and cooling in an ice-bath. To the mixture was added 2-naphthoyl chloride (1.52 g) under the same conditions. The mixture was stirred for 2 hours at the same temperature. The resultant precipitate was collected by filtration and washed with methylene chloride and water successively. The collected crystals were dried over phosphorus pentoxide under reduced pressure to give (3RS)-3-(2-naphthoylamino)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (2.33 g).

NMR (DMSO-d_6, δ) : 5.60 (1H, d, J=7.7Hz), 7.22-7.39 (5H, m), 7.54-7.66 (5H, m), 7.99-8.11 (4H, m), 8.72 (1H, s), 9.74 (1H, d, J=7.7Hz), 11.05 (1H, m)

MASS (m/e) : 423 (M^+)

Preparation 11

The following compounds were obtained according to a similar manner to that of Preparation 10.

(1) (3RS)-3-(3-Quinolylcarbonylamino)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

IR (Nujol) : 3600, 1695, 1670, 1610, 1590, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 5.59 (1H, d, J=7.6Hz), 7.23-7.40 (5H, m), 7.61-7.76 (4H, m), 7.67-7.94 (1H, m), 8.1-8.16 (2H, m), 9.09 (1H, s), 9.40 (1H, d, J=2.1Hz), 10.1 (1H, d, J=7.6Hz), 11.08 (1H, s)

(2) (3RS)-3-(3,4-Dichlorobenzoylamino)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

NMR (DMSO-d_6, δ) : 5.49 (1H, d, J=7.6Hz), 7.2-8.02 (11H, m), 8.21 (1H, s), 9.93 (1H, d, J=7.6Hz), 11.03 (1H, s)

MASS (m/e) : 442 (M^+)

Example 1

To a solution of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-[(1-tritylimidazol-4-yl)methyl]-2H-1,4-benzodiazepin-2-one (1.0 g) in N,N-dimethylformamide (10 ml) were added successively (E)-3-(2-nitrophenyl)propenoic acid (330 mg), 1-hydroxybenzotriazole (230 mg), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (320 mg) and triethylamine (170 mg) under stirring at ambient temperature. The mixture was stirred for 3 hours and allowed to stand overnight. The reaction mixture was poured into a mixture of ethyl acetate and water under stirring. The separated organic layer was washed with water twice and dried. The solvent was removed under reduced pressure to give an amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was pulverized and stirred for several hours in diisopropyl ether. Collection by filtration, washing with diisopropyl ether and drying under reduced pressure gave (3S)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[(E)-3-(2-nitrophenyl)propenoylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.16 g).

NMR ($CDCl_3$, δ) : 5.07 (2H, br s), 5.66-5.7 (1H, m), 6.49-8.14 (32H, m)

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) (3S)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[(2-amino-4-chlorobenzoyl)amino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

NMR ($CDCl_3$, δ) : 5.06 (2H, d, J=3.7Hz),

5.62-5.68 (3H, m), 6.63-8.04 (29H, m)
MASS (m/e) : 502 (M^+-243)

(2) (3RS)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[(2,3,4,5-tetrahydro-3-oxopyridazin-6-yl)-carbonylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

(3) (3RS)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-(3,4-dichlorobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one·
NMR ($CDCl_3$, δ) : 5.02 (1H, d, J=15Hz), 5.12 (1H, d, J=15Hz), 5.67 (1H, d, J=7.8Hz), 6.85-8.04 (29H, m)

(4) (3RS)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one
NMR (DMSO-d_6, δ) : 5.01-5.18 (2H, m), 5.78 (1H, d, J=7.8Hz), 6.87-8.26 (30H, m), 8.72 (1H, d, J=1.9Hz), 9.44 (1H, d, J=2.2Hz)
MASS (m/e) : 504 (M^+-243), 424

(5) (3RS)-1,3-Dihydro-1-[(1-tritylimiazol-4-yl)methyl]-3-(2-quinoxalinylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

(6) (3RS)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-(4-cinnolinylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one
NMR ($CDCl_3$, δ) : 5.09 (2H, s), 5.80 (1H, d,J=7.8Hz), 6.86-8.09 (28H, m), 8.49-8.66 (2H, m), 9.54 (1H, s)

(7) (3RS)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-

3-(1-isoquinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

NMR ($CDCl_3$, δ) : 5.11 (2H, s), 5.78 (1H, d, J=8.3Hz), 6.89-7.89 (28H, m), 8.05 (1H, d, J=8.2Hz), 8.59 (1H, d, J=5.5Hz), 9.52-9.56 (1H, m), 9.93 (1H, d, J=8.2Hz)

(8) (3RS)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-nicotinoylamino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

NMR ($CDCl_3$, δ) : 4.99-5.16 (4H, m), 5.71 (1H, d, J=7.7Hz), 6.85-9.18 (28H, m)

Example 3

To a solution of (3RS)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.0 g) in methylene chloride (10 ml) were added successively triethylamine (340 mg) and 2-naphthoyl chloride (320 mg). The mixture was stirred for 1.5 hours. The reaction mixture was washed with water and dried. The solvent was removed under reduced pressure to give an amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford on oil, which was dried under reduced pressure to give (3RS)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-(2-naphthoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.21 g).

NMR ($CDCl_3$, δ) : 5.03 (2H, d, J=15Hz), 5.15 (2H, d, J=15Hz), 5.79 (1H, d, J=8Hz), 6.89-8.07 (29H, m), 8.22 (1H, d, J=8Hz), 8.47 (1H, s)

Example 4

To a solution of (3RS)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-amino-5-(2-fluorophenyl)-2H-

1,4-benzodiazepin-2-one (1.5 g) in tetrahydrofuran (23 ml) was added m-tolyl isocyanate (0.35 g) under stirring at ambient temperature. The mixture was stirred for 2 hours under the same condition. From the reaction mixture, the solvent was removed in vacuo to give crude product, which was recrystallized from a mixture of ethyl acetate and tetrahydrofuran to afford pure (3RS)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[3-(3-methylphenyl)ureido]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.47 g).

NMR (DMSO-d_6, δ) : 2.24 (3H, s), 4.85 (1H, d, J=14.8Hz), 5.24-5.33 (2H, m), 6.67-7.68 (29H, m), 7.91 (1H, d, J=8.2Hz), 8.97 (1H, s)

Example 5

To a suspended mixture of iron powder (1.1 g) and ammonium chloride (0.13 g) in a mixture of water (2.5 ml) and ethanol (7.5 ml) was added portionwise (3S)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[(E)-3-(2-nitrophenyl)propenoylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.1 g) under stirring and refluxing. After ethanol (7.5 ml) and water (2.5 ml) were added, the resultant mixture was refluxed under stirring for 1.5 hours. The reaction mixture was filtered through celite and the filtered mass was washed with hot ethanol several times. From the filtrate and the washings, ethanol was removed under reduced pressure. To the residual mixture was added a saturated aqueous solution of sodium bicarbonate (100 ml) and the mixture was extracted with ethyl acetate (100 ml). After washing with water and drying over magnesium sulfate, the extract was evaporated to give an amorphous residue, which was pulverized with diisopropyl ether and collected by filtration to afford (3S)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[(E)-3-(2-aminophenyl)propenoylamino]-5-(2-fluorophenyl)-

2H-1,4-benzodiazepin-2-one (0.98 g).

NMR ($CDCl_3$, δ) : 3.71-4.07 (2H, br d), 5.06 (2H, s), 5.68 (1H, d, J=8Hz), 6.47-7.99 (32H, m)

MASS (m/e) : 476 (M^+-260)

Example 6

To a solution of (3S)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-[(E)-3-(2-aminophenyl)-propenoylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (0.49 g) in N,N-dimethylformamide (4.9 ml) was added 6N-hydrochloric acid (3.4 ml) under stirring and cooling in an ice-bath. The mixture was warmed to 50°C and stirred for 1 hour. After cooling to room temperature, to the reaction mixture were added water and ethyl acetate under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried. The solvent was removed under reduced pressure to give an amorphous residue, which was pulverized and stirred for several hours in diisopropyl ether. Collection by filtration, washing with diisopropyl ether and drying under reduced pressure gave (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-[(E)-3-(2-aminophenyl)propenoylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (350 mg). To a solution of the product obtained above in chloroform (10 ml) was added 20%-hydrogen chloride in ethanol (5 ml) under cooling. The clear yellow solution was evaporated to dryness under reduced pressure. The residue was pulverized and stirred for several hours in diisopropyl ether. Collection by filtration, washing with diisopropyl ether and drying under reduced pressure gave yellow powder (234 mg) of (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-[(E)-3-(2-aminophenyl)propenoylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride.

IR (Nujol) : 3650-3050, 2700-2150, 1660, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 3.8-4.8 (2H, b), 5.15-5.56 (3H, m), 7.04-7.81 (18H, m), 9.03 (1H, s), 9.43 (1H, d, J=8Hz)

MASS (m/e) : 494 (M^+-73), 476

Example 7

The following compounds were obtained according to a similar manner to that of Example 6.

(1) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-[(2-amino-4-chlorobenzoyl)amino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

mp : 180-220°C (dec.)

IR (Nujol) : 3500-3000, 1675, 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 4.93 (1H, d, J=15Hz), 5.20 (1H, d, J=15Hz), 5.25-5.69 (3H, m), 6.62-6.67 (2H, m), 6.98-7.26 (6H, m), 7.40-7.69 (5H, m), 7.89-7.91 (2H, m)

MASS (m/e) : 502 (M^+)

(2) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-[(2,3,4,5-tetrahydro-3-oxopyridazin-6-yl)carbonylamino]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride

mp : 230-240°C (dec.)

IR (Nujol) : 3650-3050, 2650, 2200, 1670, 1610, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.41-2.88 (4H, m), 5.20 (1H, d, J=16Hz), 5.42 (1H, d, J=16Hz), 5.43 (1H, d, J=7.8Hz), 7.15-7.78 (9H, m), 8.58 (1H, d, J=7.8Hz), 9.02 (1H, s), 11.31 (1H, s), 14.67 (1H, br s)

MASS (m/e) : 393 (M^+-153)

(3) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(3,4-

dichlorobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one hydrochloride

mp : 212-230°C (dec.)

IR (Nujol) : 3650, 3150, 2650-2000, 1650, 1600, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 5.20 (1H, d, J=16Hz), 5.43 (1H, d, J=16Hz), 5.61 (1H, d, J=7.3Hz), 7.19-7.82 (10H, m), 7.98 (1H, dd, J=2Hz, 8Hz), 8.30 (1H, d, J=2Hz), 9.02 (1H, d, J=1.2Hz), 10.0 (1H, d, J=9.4Hz), 14.64 (1H, br s)

MASS (m/e) : 521 (M^+-37), 441

(4) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride

mp : 230-233°C (dec.)

IR (Nujol) : 3600-3100, 2700-2100, 1670, 1610, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 5.24 (1H, d, J=16Hz), 5.47 (1H, d, J=16.1Hz), 5.71 (1H, d, J=7.2Hz), 7.2-8.39 (13H, m), 9.05 (1H, d, J=1.1Hz), 9.48 (1H, d, J=1.8Hz), 9.60 (1H, d, J=2Hz), 10.36 (1H, d, J=7.2Hz), 14.72 (1H, br s)

MASS (m/e) : 504 (M^+-73), 424

(5) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-quinoxalinylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one hydrochloride

mp : 205-220°C (dec.)

IR (Nujol) : 3600-3050, 2700-2000, 1670, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 5.25 (1H, d, J=16.1Hz), 5.48 (1H, d, J=16.1Hz), 5.68 (1H, d, J=7.8Hz), 7.18-8.35 (13H, m), 9.04 (1H, s), 9.53-9.61 (2H, m), 14.63 (1H, m)

MASS (m/e) : 505 (M^+-36), 425

(6) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(4-cinnolinylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride
mp : 215-230°C (dec.)
IR (Nujol) : 3600-3100, 2700-2100, 1660, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 5.21-5.72 (3H, m), 7.18-8.61 (13H, m), 9.01 (1H, s), 9.48 (1H, s), 10.46 (1H, d, J=7.1Hz), 14.61 (1H, br s)
MASS (m/e) : 505 (M^+-73), 448

(7) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(1-isoquinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride
mp : 209-220°C (dec.)
IR (Nujol) : 3600-3200, 2700-2100, 1670, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 5.2-5.55 (2H, m), 5.67 (1H, d, J=7.7Hz), 7.23-8.19 (13H, m), 8.67 (1H, d, J=5.6Hz), 9.03 (1H, s), 9.19 (1H, d, J=8.4Hz), 9.9 (1H, d, J=7.7Hz), 14.62 (1H, br s)
MASS (m/e) : 504 (M^+-73), 424

(8) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-nicotinoylamino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one dihydrochloride
mp : 220-235°C (dec.)
NMR (DMSO-d_6, δ) : 5.21 (1H, d, J=16.1Hz), 5.45 (1H, d, J=16.1Hz), 5.64 (1H, d, J=7.2Hz), 7.2-8.0 (1H, m), 8.76-9.04 (2H, m), 9.32 (1H, s), 10.32 (1H, d, J=7.2Hz), 14.67 (1H, br s)
MASS (m/e) : 454 (M^+-73)

(9) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-naphthoylamino)-5-(2-fluorophenyl)-2H-1,4-

benzodiazepin-2-one hydrochloride
mp : 220-230°C (dec.)
IR (Nujol) : 3600-3050, 2800-2000, 1690, 1660, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 5.22 (1H, d, J=16Hz), 5.45 (1H, d, J=16Hz), 5.70 (1H, d, J=7.4Hz), 7.19-8.1 (15H, m), 8.70 (1H, s), 9.03 (1H, s), 9.78 (1H, d, J=7.4Hz), 14.61 (1H, br s)
MASS (m/e) : 503 (M^+-37), 427

(10) (3RS)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-[3-(3-methylphenyl)ureido]-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one hydrochloride
mp : 210-225°C (dec.)
IR (Nujol) : 3600-3050, 1680, 1610, 1555 cm^{-1}
NMR (DMSO-d_6, δ) : 2.24 (3H, s), 5.06 (2H, s), 5.26 (1H, d, J=8.4Hz), 6.74 (1H, d, J=6.6Hz), 6.87 (1H, s), 7.07-7.71 (13H, m), 8.02 (1H, d, J=8.0Hz), 8.99 (1H, s)

Example 8

To a mixture of (3RS)-1,3-dihydro-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (850 mg) and 1-trityl-4-(2-chloroethyl)imidazole monohydrochloride (900 mg) in N,N-dimethylformamide were added sodium hydride (60% suspension in mineral oil, 180 mg) and sodium iodide (3.98 g) under stirring and cooling at 0°C in an ice-salt bath in a stream of nitrogen. The mixture was stirred at room temperature for 1.5 hours and at 60-65°C for 6 hours. Acetic acid (2 ml) was added to the reaction mixture. The resultant mixture was poured into a mixture of ethyl acetate (200 ml) and water (200 ml) under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water. The solvent was

removed under reduced pressure to give an amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was dried under reduced pressure to give (3RS)-1,3-dihydro-1-[2-(1-tritylimidazol-4-yl)ethyl]-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (750 mg).

NMR (DMSO-d_6, δ) : 2.49-2.65 (2H, m), 3.8-4.6 (2H, m), 5.62 (1H, d, J=7.48Hz), 6.70 (1H, s), 7.00-8.1 (28H, m),.9.05 (1H, s), 9.35 (1H, d, J=2.2Hz), 10.0 (1H, d, J=7.64Hz)

Example 9

To a solution of (3RS)-1,3-dihydro-3-(2-naphthoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.25 g) in N,N-dimethylformamide (31 ml) was added sodium hydride (60% suspension in mineral oil, 130 mg) under stirring and cooling at 0°C in an ice-salt bath in a stream of nitrogen. After the mixture was stirred at room temperature for 45 minutes, a solution of chloroacetonitrile (270 mg) in N,N-dimethylformamide (5 ml) was added to the mixture at 0°C under stirring. The resultant mixture was stirred overnight at room temperature. Acetic acid (0.5 g) was added to the reaction mixture. The resultant mixture was poured into a mixture of ethyl acetate (200 ml) and water (300 ml) under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water. The solvent was removed under reduced pressure to give amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was dried under reduced pressure

to give (3RS)-1,3-dihydro-1-cyanomethyl-3-(2-naphthoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.19 g).

NMR (DMSO-d_6, δ) : 5.08-5.32 (2H, m), 5.74 (1H, d, J=7.65Hz), 7.25-7.82 (14H, m), 8.71 (1H, s), 9.95 (1H, d, J=7.68Hz)

Example 10

The following compounds were obtained according to similar manners to those of Examples 8 and 9.

(1) (3RS)-1,3-Dihydro-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one

mp : 284-285°C

IR (Nujol) : 3400, 1695, 1650, 1600, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 5.4-5.62 (2H, m), 5.76 (1H, d, J=7.74Hz), 7.23-7.39 (4H, m), 7.63-7.79 (4H, m), 7.86-7.93 (2H, m), 8.09-8.32 (2H, m), 9.05 (1H, s), 9.37 (1H, d, J=2.36Hz), 10.12 (1H, d, J=7.78Hz), 15.2-16.0 (1H, br s)

MASS (m/e) : 507 (M^+), 424 (M^+-83)

(2) (3RS)-1,3-Dihydro-3-(3,4-dichlorobenzoylamino)-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one

mp : 260-265°C (dec.)

IR (Nujol) : 3600, 3050, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.83 (1H, br s), 5.2-5.4 (2H, m), 5.63 (1H, d, J=7.8Hz), 7.14-7.33 (5H, m), 7.55-7.67 (4H, m), 7.77 (1H, d, J=8.4Hz), 7.97 (2H, d, J=8.4Hz), 8.?8 (1H, d, J=1.9Hz), 9.94 (1H, d, J=7.83Hz)

MASS (m/e) : 524 (M^+), 368 (M^+-156)

(3) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one
mp : 280-290°C (dec.)
IR (Nujol) : 3150, 1640, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 5.21-5.3 (2H, m), 5.69 (1H, d, J=8.14Hz), 7.02-7.66 (13H, m), 7.97 (1H, d, J=8.26Hz), 9.52 (1H, d, J=8.18Hz), 11.67 (1H, s)
MASS (m/e) : 351 (M^+-144), 332 (M^+-162)

(4) (3RS)-1,3-Dihydro-1-[2-(4-imidazolyl)ethyl]-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one
mp : 165-175°C (dec.)
IR (Nujol) : 3600-3000, 1650, 1600 cm^{-1}

(5) (3S)-3-(2-Indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one
NMR (DMSO-d_6, δ) : 5.49 (2H, ABq, J=16.4Hz, 24.8Hz), 5.73 (1H, d, J=8.0Hz), 7.0-7.91 (14H, m), 9.60 (1H, d, J=8.0Hz), 11.65 (1H, s)

Example 11

To a solution of (3RS)-1,3-dihydro-1-[2-(1-trityl-imidazol-4-yl)ethyl]-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (740 mg) in N,N-dimethylformamide (7.4 ml) was added 6N-hydrochloric acid (5.18 ml) under stirring and cooling in an ice-bath. The mixture was warmed to 60-70°C and stirred for one hour. After cooling to room temperature, to the reaction mixture were added ice water and ethyl acetate under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried.

The solvent was removed under reduced pressure to give an amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was pulverized and stirred for several hours in diisopropyl ether. The precipitate was collected by filtration, washed with diisopropyl ether and dried under reduced pressure to give (3RS)-1,3-dihydro-1-[2-(4-imidazolyl)-ethyl]-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (0.25 g).

mp : 165-175°C (dec.)

IR (Nujol) : 3600-3000, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.52-2.66 (2H, m), 4.09-4.63 (2H, m), 5.65 (1H, d, J=7.6Hz), 6.77 (1H, s), 7.24-8.32 (13H, m), 9.07 (1H, d, J=1.92Hz), 9.39 (1H, d, J=2.2Hz), 10.11 (1H, d, J=7.6Hz), 11.82 (1H, br s)

MASS (m/e) : 518 (M^+)

Example 12

To a mixture of (3RS)-1,3-dihydro-3-(3,4-dichloro-benzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (500 mg) and 1-trityl-4-(2-chloroethyl)imidazole monohydrochloride (295 mg) in N,N-dimethylformamide (7.5 ml) were added sodium hydride (60% suspension in mineral oil, 99.5 mg) and sodium iodide (2.25 g) under stirring and cooling at 0°C in an ice-salt bath in a stream of nitrogen. After the mixture was stirred at room temperature for 1.5 hours and at 60-65°C for 6 hours. To the reaction mixture were added acetic acid (1.1 ml) and 6N-hydrochloric acid (5 ml) and the mixture was stirred at 60-70°c for one hour. The resultant mixture was poured into a mixture of ethyl acetate (100 ml) and water (100 ml) under stirring. The mixture was adjusted to pH 8 with

an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried. The solvent was removed under reduced pressure to give an amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was pulverized and stirred for several hours in diisopropyl ether. Collection by filtration, washing with diisopropyl ether and drying under reduced pressure gave (3RS)-1,3-dihydro-1-[2-(4-imidazolyl)ethyl]-3-(3,4-dichlorobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (0.18 g).

mp : 149-159°C

IR (Nujol) : 3600-3100, 1650, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.5-2.59 (2H, m), 3.95-4.62 (2H, m), 5.5 (1H, d, J=7.52Hz), 6.77 (1H, br s), 7.23-8.32 (12H, m), 9.99 (1H, br s), 11.8 (1H, br s)

MASS (m/e) : 386 (M^+-150)

Example 13

The following compounds were obtained according to a similar manner to that of Example 12.

(1) (3RS)-1,3-Dihydro-1-[2-(4-imidazolyl)ethyl]-3-(2-naphthoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

mp : 198-205°C (dec.)

IR (Nujol) : 3275, 1680, 1630, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 2.5-2.8 (2H, m), 4.0-4.6 (2H, m), 5.65 (1H, d, J=7.67Hz), 6.81 (1H, br s), 7.24-8.09 (15H, m), 8.71 (1H, s), 9.78 (1H, d, J=7.71Hz), 11.8 (1H, br s)

MASS (m/e) : 518 (M^+)

(2) (3RS)-1,3-Dihydro-1-[2-(4-imidazolyl)ethyl]-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

mp : 188-205°C (dec.)

IR (Nujol) : 3550-3100, 1640, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51-2.65 (2H, m), 4.01-4.08 (1H, m), 4.50-4.57 (1H, m), 5.63 (1H, d, J=7.9Hz), 6.56 (1H, s), 6.76-7.81 (14H, m), 9.60 (1H, d, J=7.9Hz), 11.64 (1H, s), 11.81 (1H, br s)

Example 14

(1) A mixture of (3RS)-1,3-dihydro-1-cyanomethyl-3-(2-naphthoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.15 g), sodium azide (480 mg) and triethylamine monohydrochloride (510 mg) in 1-methyl-2-pyrrolidinone (20 ml) was stirred at 145°C for 3.5 hours. The reaction mixture was poured into 5°C hydrochloric acid (100 ml) under stirring. The resultant precipitates were collected by filtration, washed with water and purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was pulverized and stirred for several hours in diisopropyl ether. Collection by filtration, washing with diisopropyl ether and drying under reduced pressure gave (3RS)-1,3-dihydro-3-(2-naphthoylamino)-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (540 mg).

mp : 265-275°C (dec.)

IR (Nujol) : 3570-3100, 1650, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 5.33 (2H, s), 5.73 (1H, d, J=7.98Hz), 7.18-8.09 (15H. m), 8.69 (1H, s), 9.72 (1H, d, J=8Hz)

MASS (m/e) : 505 (M^+)

The following compound was obtained according to a similar manner to that of Example 14(1).

(2) (3S)-3-(2-Indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one

NMR (DMSO-d_6, δ) : 5.49 (2H, ABq, J=16.4Hz, 24.8Hz), 5.73 (1H, d, J=8.0Hz), 7.0-7.91 (14H, m), 9.60 (1H, d, J=8Hz), 11.65 (1H, s)

Example 15

4-Chlorophenyl isocyanate (0.14 g) was added to a solution of (3RS)-3-amino-1,3-dihydro-5-phenyl-1-[(1-trityl-1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one (0.50 g) in dry tetrahydrofuran (10 ml) at room temperature. After the mixture was stirred for 3 hours, 8.4N-ethanolic hydrogen chloride (1.5 ml) was added to the mixture at room temperature and then the mixture was stirred for 3 hours. The solvent was removed under reduced pressure. The residue was suspended with a mixture of ethanol and ethyl acetate and the resultant precipitate was collected by filtration to give (3RS)-1,3-dihydro-3-[3-(4-chlorophenyl)ureido]-5-phenyl-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one monohydrochloride (0.40 g).

mp : 205-208°C

IR (Nujol) : 3325, 3250, 3190, 2725, 1690, 1600, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 5.30-5.50 (1H, m), 5.46 (2H, ABq, J=17Hz, 24Hz), 7.20-7.85 (15H, m), 9.0-11.0 (1H, broad), 9.42 (1H, s)

Example 16

The following compounds were obtained according to a similar manner to that of Example 15.

(1) (3RS)-1,3-Dihydro-3-[3-(4-chlorophenyl)ureido]-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one monohydrochloride
mp : 203-205°C
IR (Nujol) : 3320, 3250, 3190, 2720, 1695, 1605, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 5.30-5.40 (1H, m), 5.48 (2H, ABq, J=17Hz, 21Hz), 7.20-7.80 (13H, m), 8.0-10.5 (2H, broad), 9.37 (1H, s)

(2) (3RS)-1,3-Dihydro-3-[3-(3-methylphenyl)ureido]-5-phenyl-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one monohydrochloride
mp : 188-194°C (dec.)
IR (Nujol) : 3290, 2720, 2605, 1685, 1610, 1595, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 2.24 (3H, s), 5.30-5.48 (1H, m), 5.46 (2H, ABq, J=17Hz, 25Hz), 6.70-6.80 (1H, m), 7.00-7.54 (12H, m), 7.70-7.80 (2H, m), 8.0-10.20 (2H, broad), 9.12 (1H, s)

(3) (3RS)-1,3-Dihydro-5-(2-fluorophenyl)-3-[3-(3-methylphenyl)ureido]-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one monohydrochloride
mp : 181-191°C (dec.)
IR (Nujol) : 3300, 2710, 2610, 1690, 1595, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 2.24 (3H, s), 5.35-5.45 (1H, m), 5.48 (2H, ABq, J=11Hz, 22Hz), 6.70-6.78 (1H, m), 7.05-7.38 (7H, m), 7.50-7.81 (6H, m), 8.0-10.4 (2H, broad), 9.11 (1H, s)

Example 17

To a solution of (3S)-1,3-dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-(3,4-dichlorobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (20.34 g) in

N,N-dimethylformamide (204 ml) was added 6N-hydrochloric acid (157 ml) under stirring and cooling in an ice-bath. The mixture was warmed to 70-80°C and stirred for 1 hour. After cooling to room temperature, to the reaction mixture were added ice water and ethyl acetate under stirring. The mixture was adjusted to pH 8.0 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried. The solvent was removed under reduced pressure to give an amorphous residue, which was purified by column chromatography on silica gel with an eluent of chloroform. The fractions containing the desired product were combined and evaporated to afford an amorphous mass, which was dried under reduced pressure to give (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(3,4-dichlorobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one. This was dissolved in chloroform (200 ml) and to the resultant solution was added 20%-hydrogen chloride in ethanol (50 ml) under cooling. The clear yellow solution was evaporated to dryness under reduced pressure to give an amorphous mass, which was lyophirized to give (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(3,4-dichlorobenzoyl-amino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one hydrochloride as yellow powder (12.97 g).

IR ($CHCl_3$) : 3000, 2900-2200, 1660, 1600, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 5.19 (1H, d, J=16Hz), 5.43 (1H, d, J=16Hz), 5.61 (1H, d, J=7.3Hz), 7.19-7.39 (5H, m), 7.56-7.82 (5H, m), 7.95-8.00 (1H, m), 8.30 (1H, d, J=1.9Hz), 9.01 (1H, s), 9.99 (1H, d, J=7.3Hz), 14.6 (1H, br s)

MASS (m/e) : 521 (M^+-37)

$[\alpha]_D^{30}$ = -24.75° (C=0.832, CH_3OH)

Example 18

To a suspension of 2-indolecarboxylic acid (161.2 mg)

in methylene chloride (3.25 ml) was added thionyl chloride (119.0 mg) and one drop of N,N-dimethylformamide under stirring at ambient temperature. The mixture was refluxed for 1 hour with stirring. To a solution of (3S)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one hydrochloride (387.8 mg) and triethylamine (506.0 mg) in methylene chloride (8 ml) was added dropwise the solution of 2-indolylcarbonyl chloride in methylene chloride obtained above under ice-cooling and stirring. The mixture was stirred under the same conditions for 3 hours. To the reaction mixture was added chloroform. The mixture was washed with diluted hydrochloric acid and water successively and dried over magnesium sulfate. Removal of the solvent in vacuo afforded an amorphous mass, which was suspended with stirring in diisopropyl ether. The resultant powder was collected by filtration, washed with diisopropyl ether and dried under reduced pressure to give (3S)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one.

mp : 270-271°C (dec.)

$[\alpha]_D^{28.5}$ = -18.87° (C=0.62, tetrahydrofuran)

NMR (DMSO-d_6, δ) : 5.49 (2H, ABq, J=16.4Hz, 24.8Hz), 5.73 (1H, d, J=8.0Hz), 7.0-7.91 (14H, m), 9.60 (1H, d, J=8.0Hz), 11.65 (1H, s)

MASS (m/e) : 494 (M^+)

Example 19

the following compound was obtained according to a similar manner to that of Example 18.

(3R)-3-(2-Indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one

mp : 270-271°C (dec.)
$[\alpha]_D^{28.5}$: +18.72° (C=0.625, tetrahydrofuran)
NMR (DMSO-d_6, δ) : 5.49 (2H, ABq, J=16.3Hz, 24.7Hz), 5.73 (1H, d, J=8.0Hz), 7.0-7.91 (14H, m), 9.60 (1H, d, J=8.0Hz), 11.65 (1H, s)
MASS (m/e) : 494 (M^+)

Example 20

The following compounds were obtained according to a similar manner to that of Example 1.

(1) (3S)-1,3-Dihydro-1-[(1-tritylimidazol-4-yl)methyl]-3-(3,4-dichlorobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one
NMR ($CDCl_3$, δ) : 5.02 (1H, d, J=15Hz), 5.11 (1H, d, J=15Hz), 5.67 (1H, d, J=7.8Hz), 6.84-8.04 (29H, m)

(2) (3RS)-1,3-Dihydro-1-[2-(4-imidazolyl)ethyl]-3-(3-quinolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one
mp : 165-175°C (dec.)
IR (Nujol) : 3600-3000, 1650, 1600 cm^{-1}

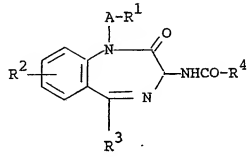
Example 21

The following compound was obtained according to a similar manner to that of Example 11.

(3S)-3-(2-Indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one
NMR (DMSO-d_6, δ) : 5.49 (2H, ABq, J=16.4Hz, 24.8Hz), 5.73 (1H, d, J=8.0Hz), 7.0-7.91 (14H, m), 9.60 (1H, d, J=8.0Hz), 11.65 (1H, s)

C L A I M S

1. A compound of the formula :



wherein R^1 is heterocyclic group which may have one or more suitable substituent(s), or cyano,

R^2 is hydrogen or halogen,

R^3 is aryl which may have one or more suitable substituent(s),

R^4 is aryl which may have one or more suitable substituent(s), ar(lower)alkenyl which may have one or more suitable substituent(s), arylamino which may have one or more suitable substituent(s), heteromonocyclic group which may have one or more suitable substituent(s), quinolyl, isoquinolyl, cinnolinyl, indolyl, or quinoxalinyl, and

A is lower alkylene,

with proviso that when R^4 is indolyl, then

(i) R^1 is tetrazolyl which may have one or more suitable substituent(s) and R^3 is halophenyl or

(ii) R^1 is imidazolyl which may have one or more suitable substituent(s), R^3 is halophenyl and

A is ethylene,
and a pharmaceutically acceptable salt thereof.

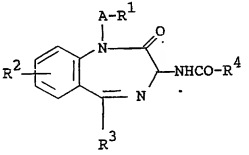
2. A compound of claim 1, wherein
R^1 is tetrazolyl which may have an imino protective group, imidazolyl which may have an imino protective group, or cyano,
R^3 is phenyl or halophenyl,
R^4 is phenyl or naphthyl, each of which may have one or two substituent(s) selected from the group consisting of halogen and amino; phenyl(lower)alkenyl which may have amino or nitro; phenylamino which may have lower alkyl or halogen; pyridyl; tetrahydropyridazinyl which may have an oxo group; quinolyl; isoquinolyl; cinnolinyl; indolyl; or quinoxalinyl.

3. A compound of claim 2, wherein
R^1 is tetrazolyl which may have mono(or di or tri)-phenyl(lower)alkyl, imidazolyl which may have mono(or di or tri)phenyl(lower)alkyl, or cyano,
R^4 is naphthyl; dihalophenyl; phenyl having halogen and amino; nitrophenyl(lower)alkenyl; aminophenyl(lower)alkenyl; lower alkylphenylamino; halophenylamino; pyridyl; tetrahydropyridazinyl having an oxo group; quinolyl; isoquinolyl; cinnolinyl; indolyl; or quinoxalinyl.

4. A compound of claim 3, wherein
R^1 is tetrazolyl,
R^2 is hydrogen,
R^3 is halophenyl,
R^4 is indolyl and
A is C_1-C_4 alkylene.

5. A compound of claim 4, which is (3S)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-[(1H-tetrazol-5-yl)methyl]-2H-1,4-benzodiazepin-2-one

6. A process for preparing a compound of the formula :



wherein R^1 is heterocyclic group which may have one or more suitable substituent(s), or cyano,

R^2 is hydrogen or halogen,

R^3 is aryl which may have one or more suitable substituent(s),

R^4 is aryl which may have one or more suitable substituent(s), ar(lower)alkenyl which may have one or more suitable substituent(s), arylamino which may have one or more suitable substituent(s), heteromonocyclic group which may have one or more suitable substituent(s), quinolyl, isoquinolyl, cinnolinyl, indolyl, or quinoxalinyl, and

A is lower alkylene,

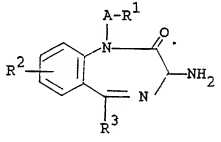
with proviso that when R^4 is indolyl, then

(i) R^1 is tetrazolyl which may have one or more suitable substituent(s) and

R^3 is halophenyl or

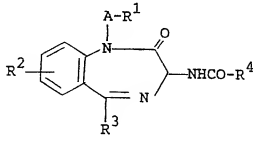
(ii) R^1 is imidazolyl which may have one or more suitable substituent(s),
R^3 is halophenyl and
A is ethylene,
or a salt thereof,
which comprises

(1) reacting a compound of the formula :



wherein R^1, R^2, R^3 and A are each as defined above,
or its reactive derivative at the amino group,
or a salt thereof with a compound of the formula :

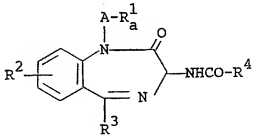
wherein R^4 is as defined above,
or its reactive derivative or a salt thereof to give a compound of the formula :



wherein R^1, R^2, R^3, R^4 and A are each as defined above,

or a salt thereof, or

(2) subjecting a compound of the formula :



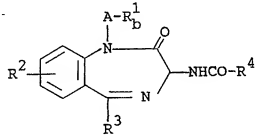
wherein R^2, R^3, R^4 and A are each as defined above, and

R^1_a is heterocyclic group having a protected imino group of the formula :

(in which R^6 is imino protective group)

in its hetero ring, which may have one or more suitable substituent(s),

or a salt thereof to elimination reaction of the imino protective group to give a compound of the formula :



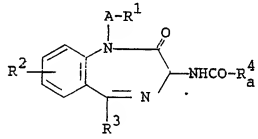
wherein R^2, R^3, R^4 and A are each as defined above, and

R^1_b is heterocyclic group having an imino group of the formula :

in its hetero ring, which may have one or more suitable substituent(s),

or a salt thereof, or

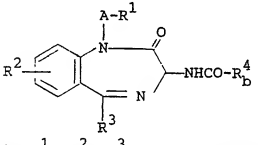
(3) subjecting a compound of the formula :



wherein R^1, R^2, R^3 and A are each as defined above, and

R_a^4 is ar(lower)alkenyl having a nitro group,

or a salt thereof to give a compound of the formula :

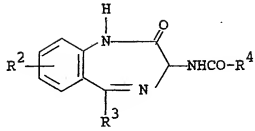


wherein R^1, R^2, R^3 and A are each as defined above, and

R_b^4 is ar(lower)alkenyl having an amino group,

or a salt thereof, or

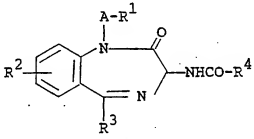
(4) reacting a compound of the formula :



wherein R^2, R^3 and R^4 are each as defined above, or a salt thereof with a compound of the formula :

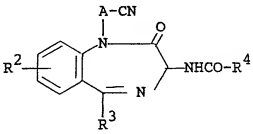
$$X\text{-}A\text{-}R^1$$

wherein R^1 and A are each as defined above, and
X is an acid residue,
or a salt thereof to give a compound of the formula :



wherein R^1, R^2, R^3, R^4 and A are each as defined above,
or a salt thereof, or

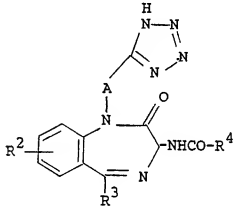
(5) reacting a compound of the formula :



wherein R^2, R^3, R^4 and A are each as defined above,
or a salt thereof with a compound of the formula :

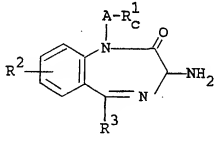
$$HN_3$$

or a salt thereof to give a compound of the formula :



wherein R^2, R^3, R^4 and A are each as defined above, or a salt thereof.

7. A compound of the formula :

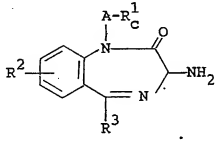


wherein R_c^1 is tetrazolyl which may have one or more suitable substituent(s),
R^2 is hydrogen or halogen,
R^3 is aryl which may have one or more suitable substituent(s), and

A is lower alkylene,

and a salt thereof.

8. A process for preparing a compound of the formula :



wherein R^1_c is tetrazolyl which may have one or more suitable substituent(s),

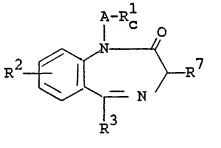
R^2 is hydrogen or halogen,

R^3 is aryl which may have one or more suitable substituent(s), and

A is lower alkylene,

or a salt thereof,

which comprises subjecting a compound of the formula:



wherein R^1_c, R^2, R^3, and A are each as defined above, and

R^7 is protected amino,

or a salt thereof to elimination reaction of the amino protective group.

9. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a

pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

10. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a cholecystokinin antagonist.

11. A method for treating or preventing cholecystokinin-mediated diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

12. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 91/00952

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 403/06, 401/14, 403/14, 243/20, A 61 K 31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]	
Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP, A2, 0349949 (FUJISAWA PHARMACEUTICAL CO., LTD.) 10 January 1990, see especially examples 33-41	1-9, 12
A	US, A, 4820834 (BEN E. EVANS ET AL.) 11 April 1989, see compound 643 and claim 1	1

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1st October 1991	26. 11. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. Pels

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

/ incompletely

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 10-11, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.

2. [X] Claim number(s) 1, because ~~they relate~~ it is/ to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of claim 1 is so broadly formulated that a very wide range of structures are included. This claim has thus not been fully searched.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/JP 91/00952

SA 49394

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/08/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0349949	10/01/90	AU-D-	3785989	11/01/90
		JP-A-	2056481	26/02/90
US-A- 4820834	11/04/89	AU-D-	1313388	15/09/88
		EP-A-	0284256	28/09/88
		JP-A-	63238069	04/10/88
		US-A-	5004741	02/04/91
		ZA-A-	8801866	06/09/88
		AU-D-	4415285	02/01/86
		EP-A-	0167919	15/01/86